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Accelerated Continuous Flow RAFT Polymerization

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ABSTRACT: Homogeneous continuous flow RAFT polymerizations with *N*-isopropylacrylamide (NIPAM) as monomer and a trithiocarbonate as chain transfer agent are investigated. Polymerization rates are considerably increased compared to reactions in batch due to more uniform heating of the solution. The fast reaction did not influence the well-defined architecture of the polymer products. PNIPAM with molecular weights of 20 kDa was produced in minutes rather than hours. The continuous polymerization is readily scalable at low operating costs.

I. Introduction

Controlled free radical polymerizations (CRP) have evolved over the last 20 years into very useful and widely applied techniques in polymer synthesis, combining the excellent control of traditional ionic living polymerizations with robust conventional free radical polymerizations.[1] Reversible addition−fragmentation chain transfer (RAFT) radical polymerizations afford, besides nitroxide mediated polymerizations (NMP) and atom transfer polymerizations (ATRP), well-defined macromolecules with low polydispersity.[2,3] Among these three basic techniques, RAFT represents the most versatile and facile method, since a variety of chain transfer agents (CTA)[4] allows for the polymerization of a wide range of monomers without the need for transition metal catalysts.[5]

In contrast to generally fast free radical polymerizations, the controlled living process requires longer reaction times. Heating by microwave irradiation can considerably shorten the reaction times, while maintaining the living character of the process.[6−11] The scale-up of batch reactions in microwave reactors is however difficult, if not impossible. Polymerizations in continuous flow offer the possibility to increase the through-put at low operating costs, and the polymer product is obtained in constant quality.[12−15] Because of the larger specific surface areas compared to batch reactors, heat transfer is enhanced in continuous flow, leading to uniform heating of the solution. In continuous flow, the mixing system allows for best control of reagents diffusion, ensuring more defined and reproducible results than in the batch process.[16,17] A scale down to screen for optimal reaction conditions without wasting precious material is also possible in continuous flow. Many polymer samples with different properties can by obtained in a single experiment within short periods of time.[18−20]

RAFT polymerizations in homogeneous solution, unlike ATRP and NMP,[21−23] have not been conducted previously in continuous flow. To date, only RAFT polymerizations in miniemulsion has been carried out both in continuous stirred tank reactors[24] and in a multitube reaction system.[25] Here, we report for the first time RAFT solution polymerizations in a continuous flow reactor. *N*-Isopropylacrylamide (NIPAM) serves as monomer and 2-dodecylsulfanylthiocarbonylsulfanyl-2-dimethylpropionic acid (DMP)[26] as chain transfer agent (CTA) (Scheme 1a).[27,28] RAFT polymerizations of acrylamides using trithiocarbonate CTAs usually lead to well-defined polymers within several hours.[3] Because of its thermoresponsive properties, PNIPAM is a widely used poly(acrylamide). Potential applications of this polymer include smart surface coatings[29] as well as temperature-sensitive hydrogels[30] that require larger amounts of material.

II. Experimental Section

Sample Preparation and Setup of the System. Continuous flow RAFT polymerizations were conducted at a monomer concentration of 2.2 M in 1,4-dioxane using 2,2′-azobis(isobutyronitrile) (AIBN) as thermal initiator in 0.1:1 ratio to the CTA. Solutions of NIPAM monomer as well as CTA and the initiator were freshly prepared under normal atmosphere. The two solutions were simultaneously injected into poly(tetrafluoroethylene) (PTFE) tubing (0.75 or 1.55 mm inner diameter (i.d.)) using a syringe pump at a constant flow rate and mixed at room temperature by a T-connection. Polymerization occurred by immersing the tubing with a volume of 3 mL (ca. 1.5 m length) behind the T-connection into a conventionally heated oil bath (Scheme 1b).

In order to screen for optimal conditions, reaction parameters such as monomer to CTA ratio (n) and temperature were systematically varied. The same reactor was used for every experiment, and the reaction time was adjusted simply via the flow rate. The continuous flow reaction was conducted safely above atmospheric pressure by using a back pressure regulator (40 psi, corresponding to the vapor pressure of 1,4-dioxane at 130 °C).

For every set of parameters, a kinetic study was performed by conducting the reaction at five different residence times that are defined by the length of the tubing and the flow rate. Product samples were characterized by size exclusion chromatography (SEC) in *N*-methylpyrrolidone (NMP) using polystyrene (PS) standards. The conversion was determined by ^{1}H NMR in DMSO-d6 from the ratio of vinyl signals of the monomer to backbone signals of the polymer (Supporting Information, Figure SI 1).

III. Results and Discussion

Screening of Conditions. PNIPAM was formed in 62% yield within only 4 min at 90 °C and a monomer to CTA ratio of 200. After 60 min residence time polymer with an apparent molecular weight $M_{n,app}$ of 21.5 kDa, close to the expected molecular weight (22.6 kDa), was obtained (Table 1, entry 1). A control experiment without CTA gave no polymer, showing that the polymerization proceeds via RAFT and not by free radical polymerization. As for RAFT polymerizations in

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Scheme 1. (a) RAFT Polymerization Synthetic Scheme of *N*-Isopropylacrylamide (NIPAM) Using 2-Dodecylsulfanylthiocarbonylsulfanyl-2-dimethylpropionic Acid (DMP) and 2,2′-Azobisisobutyronitrile (AIBN) in 1,4- Dioxane and (b) Experimental Setup of the Continuous Flow Reaction

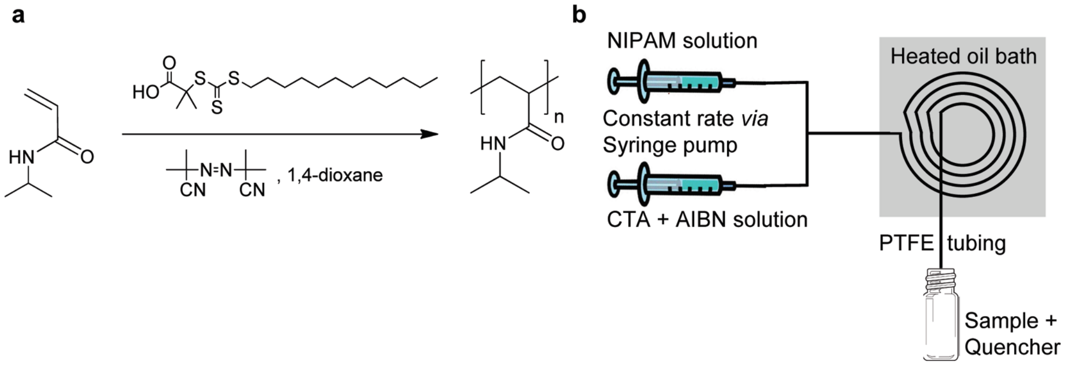


Table 1. Conversion of the RAFT Polymerization and Poly(*N*-isopropylacrylamide) (PNIPAM) Properties after 60 min at 90 °C and Comparison of Polymerization in Batch (Conventional Heating and Microwave Irradiation) and in Continuous Flow in PTFE Tubing with 0.75 mm and 1.55 mm Inner Diameter (i.d.)

entry	method	conversion (%)	$M_{n,app}$ / kDa	PDI
1	continuous flow 0.75 mm i.d.	88	21.5	1.15
2	continuous flow 1.55 mm i.d.	78	17.2	1.31
3	continuous flow 1.55 mm i.d.	79	20.0	1.31
4	conventional heating	40	13.4	1.12
5	microwave irradiation	85	19.4	1.16

batch,[27] a symmetric peak in SEC with a polydispersity (PDI) of 1.15 was observed. The narrow molecular weight distribution was not affected by potential back mixing or axial dispersion.[31] The PDI was improved to 1.11 when the reaction was carried out under an argon atmosphere (data not shown). Increasing the inner diameter of the tubing from 0.75 mm to 1.55 mm resulted in slightly lower conversions and higher PDIs (Table 1, entry 2 and 3). However, through-put was increased and the risk of clogging was diminished. The polymerization process was very reproducible (Table 1, entry 2 and 3).

For screening, the monomer to CTA ratio was systematically varied (Figure 1). As expected, the polymerization was considerably accelerated at higher CTA ratios. In all cases, polymers with predictable chain lengths and narrow, symmetric molecular weight distributions were obtained. For shorter polymers ($n \sim 50$), the 2-dodecylsulfanylthiocarbonylsulfanyl end group was clearly identified by ^{1}H NMR. For the sample after 30 min residence time, end group analysis revealed 43 repeat units, a finding that corresponds well to the SEC results ($M_{n,app} = 5.2$ kDa corresponding to 46 repeat units). For low conversions at $n = 1000$, a linear relationship of $M_{n,app}$ on conversion was found indicating that the overall concentration of polymer chains remained constant (Figure SI 2 in the Supporting Information).

By using a back pressure regulator, the continuous flow polymerization could also be safely conducted above the boiling point of the solvent. An increase in temperature from 90 to 130 °C had little effect on polymerization kinetics (Figure SI 3 in the Supporting Information). Polydispersities increased from ~1.2 to 1.3−1.6, indicating that the polymerization was less controlled. This result can be explained by an increase in radical concentration due to the faster decomposition of AIBN at higher temperatures.

Kinetics Studies. A more detailed investigation of the polymerization kinetics was conducted at 90 °C and a monomer to CTA ratio of $n = 200$, by comparing the polymerization in continuous flow to batch reactions with conventional heating and microwave irradiation, respectively.

The same stock solutions for batch and microwave experiments were used as in the polymerization in continuous flow. The reaction solutions were prepared by mixing the stock solutions (1:1 v/v) at room temperature and were then directly submitted either to an oil bath or to microwave irradiation. In both cases the mixing system considered was a magnetic stirring bar. Compared to batch polymerizations with conventional heating (volume ~20 mL), the continuous flow reaction was accelerated by a factor of about four (estimated from the initial slopes, Table 1 and Figure 2). More uniform heating of the reaction solution due to the high surface area of the tubing and better heat transfer are likely responsible. In the absence of back mixing and axial dispersion, the tubing can be regarded as a series of independent small units of volume with constant monomer and polymer chain concentrations. This pronounced homogeneity may also account for faster kinetics.

The batch reaction with microwave irradiation (MW) was also considerably faster than with conventional heating.[11] This observation has been explained by a constant and efficient energy input that results in uniform heating of the solution, and thus in an increase of both the propagation rate and the addition−fragmentation rates.[7] An additional acceleration was assigned to a dielectric heating effect which adds to this thermal effect.[6]

Continuous flow polymerization with conventional heating proceeded on a similar time as batch reactions heated by microwave irradiation (Figure 2). In both cases, conversions exceeding 60% and apparent molecular weights close to the expected molecular weight were reached within just 8 min (Figure SI 4 in the Supporting Information). At 130 °C, the polymerization under microwave irradiation was also only slightly faster than in continuous flow, thus confirming the results at 90 °C (Figure SI 5 in the Supporting Information).

Polymer Glyco-Functionalization and Microarray Studies. RAFT polymerization is convenient to obtain polymer products with well-defined end groups which can be further functionalized to serve as a tool for biochemical and biological investigations. PNIPAM was functionalized with carbohydrates to provide a tool for lectin binding on a glass slide. α-Mannose specifically binds to Concanavalin A (ConA) and served as proof-of-principle.[32] Amidation with acetylated mannose via an amino linker followed by removal of the acetyl groups and reduction of the trithioarbonate under basic conditions afforded the final compound (Scheme 2).[33] To evaluate lectin binding, the functionalized PNIPAM polymer was fixed via the thio-anchor on a glass surface previously activated with maleimido groups.

The microarray functionalized with the modified PNIPAM polymer was incubated with FITC-labeled ConA

(Concanavalin A−Fluorescein isothiocyanate). Binding was detected by fluorescent imaging (Figure 3b). The protein was washed away with Tris−HCl buffer, pH 7.4 at 40 °C, in the absence of any detergent, chaotropic agent or high ionic strength (Figure 3c) before the same slide was used for a second binding measurement (Figure 3d). Washing at 40 °C is effective since at temperatures above 32 °C the polymer chain shrinks thereby disrupting binding and facilitating the release of the proteins.[33] Thus, the same slide can be reused multiple times. At room temperature the flexibility of the long polymer chains allows for better binding when compared to short linkers (Figure 3b vs 3a).

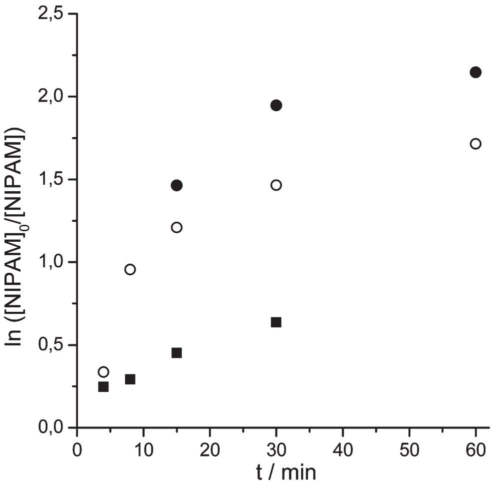


Figure 1. Pseudo-first-order plots of the continuous flow RAFT polymerization of *N*-isopropylacrylamide (NIPAM) at 90 °C and different monomers: chain transfer agent (CTA) ratios (n): $n = 50$ (●), $n = 200$ (○), and $n = 1000$ (■).

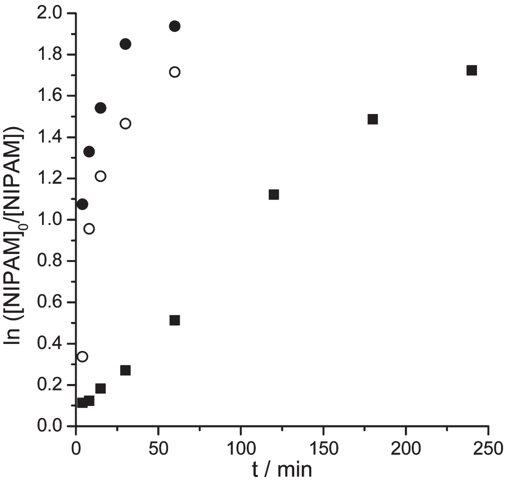


Figure 2. Pseudo first-order plots of the polymerization at 90 °C and $n = 200$ in batch with conventional heating (■), microwave irradiation (●), and conventional heating in continuous flow (○).

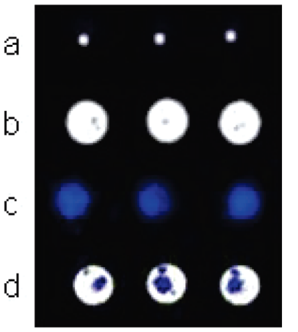


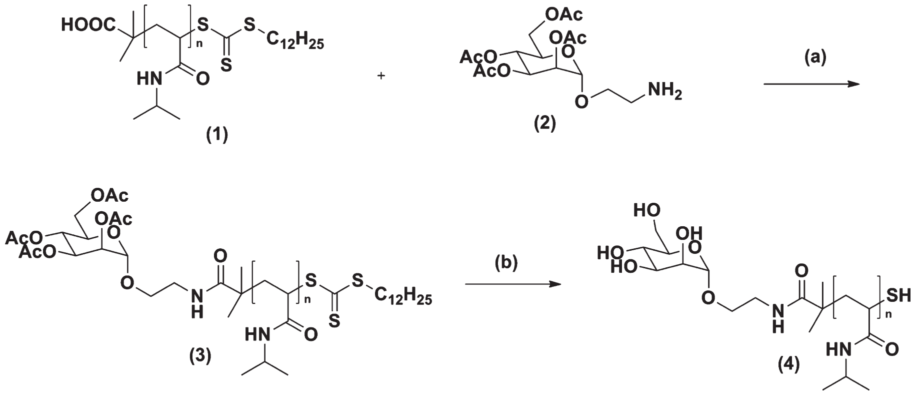
Figure 3. Glycopolymer microarray: (a) control (Man$_4$Glc-SH, 100 μM) stained with ConA-FITC (Concanavalin A−Fluorescein isothiocyanate); (b) Man-PNIPAM (**4**, 100 μM) stained with ConA-FITC after washing at room temperature; (c) Man-PNIPAM (**4**) after washing cycles at 40 °C; (d) Man-PNIPAM (**4**) stained a second time with ConA-FITC.

Binding experiments using unlabeled ConA were performed, as described above, and the wash solutions were analyzed by MALDI to identify released protein (see Figure SI 7 in the Supporting Information) and confirmed the findings detailed above.

IV. Conclusions

In summary, we describe the first homogeneous RAFT polymerization in continuous flow. The polymerization is considerably faster when compared to batch reactions. Thermo responsive PNIPAM with apparent molecular weights of ~20 kDa was obtained within minutes in flow, instead of hours in batch, while maintaining the controlled character of the polymerization. The continuous flow polymerization with conventional heating exhibits similar kinetics as under microwave irradiation. Continuous flow reactions, unlike microwave reactions, are readily scalable and allow for rapid sampling of the reaction space. The polymer can be further functionalized with carbohydrate ligands, fixed on microarray slides for multivalent display and the detection of potential lectins.

Scheme 2. Functionalization of Poly(*N*-Isopropylacrylamide) (PNIPAM) for Microarray Applications: (a) *N*,*N*-Diisopropylethylamine (DIPEA), Benzotriazol-1-yl-oxytripyrrolidinophosphonium Hexafluorophosphate (PyBOP), 1-Hydroxybenzotriazole (HOBt), Overnight, Room Temperature, DMF/DCM (1:1, 5 mL) (75%); (b) NaOMe 1 M, Overnight, Room Temperature (Quant.)



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Supporting Information Available: Description of experimental procedures and exemplary ^{1}H NMR and SEC data, as well as additional experiments on polymerization kinetics. This material is available free of charge via the Internet at http://pubs.acs.org.

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